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### Title

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### Permalink

<https://escholarship.org/uc/item/4356r0j9>

### Journal

Neuroscience letters, 497(3)

### ISSN

0304-3940

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### Publication Date

2011-06-01

### DOI

10.1016/j.neulet.2011.02.032

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Peer reviewed

Published in final edited form as:

*Neurosci Lett.* 2011 June 27; 497(3): 155–162. doi:10.1016/j.neulet.2011.02.032.

## Epileptogenesis after prolonged febrile seizures: mechanisms, biomarkers and therapeutic opportunities

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### Abstract

Epidemiological and recent prospective analyses of long febrile seizures (FS) and febrile status epilepticus (FSE) support the idea that in some children, such seizures can provoke temporal lobe epilepsy (TLE). Because of the high prevalence of these seizures, if epilepsy was to arise as their direct consequence, this would constitute a significant clinical problem. Here we discuss these issues, and describe the use of animal models of prolonged FS and of FSE to address the following questions: Are long FS epileptogenic? What governs this epileptogenesis? What are the mechanisms? Are there any predictive biomarkers of the epileptogenic process, and can these be utilized, together with information about the mechanisms of epileptogenesis, for eventual prevention of the TLE that results from long FS and FSE.

### Introduction

Febrile seizures (FS) are defined as seizures taking place during fever, but which are not a result of an invasive infection of the central nervous system. These seizures occur in infants and young children, with a median age of 11–18 months [42,88,107,112]. Fever-related seizures are very rare in normal adults, so that the ability of fever to generate seizures is generally considered a characteristic of the developing brain. In addition, the reason that FS are the most common of all childhood seizures may derive from the fact that infants and children sustain > 6 febrile episodes per year, so that fever is more common than other potential seizure-provoking insults such as trauma or hyponatremia.

FS, both short and long, may occur in both normal children and those with a predisposition to the seizures and to the development of epilepsy, such as ion channel mutations or cortical dysplasia. However, studies indicate that even identical twins may diverge in the presence of long FS and the development of temporal lobe epilepsy (TLE), suggesting that the occurrence of FSE in itself might be epileptogenic in the non-predisposed brain [60]. However, whereas twin studies provide a valuable tool, it is difficult to control clinical studies for host-brain variability. Therefore, discovering if long FS or FSE are sufficient to provoke epilepsy requires controlled experimental models. Here we focus on the following points:

- A. Are prolonged FS and febrile status epilepticus (FSE) epileptogenic?

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- B. What is the role of predisposing elements of the host brain, such as gene mutations, cortical dysplasia, in FS-induced epileptogenesis?
- C. What parameters of the FS themselves (duration, severity) govern the development of epilepsy?
- D. How does epilepsy arise after FS? Several mechanisms (cell loss, inflammation and altered patterns of gene expression) have been implicated in epileptogenesis.
- E. Are there predictive biomarkers of epileptogenesis?
- F. What therapeutic strategies can be used for preventing and/or reversing FS-induced epileptogenesis?

For each of these points, we briefly describe available information from clinical studies, followed by contributions of experimental approaches.

### A. Are prolonged FS and FSE epileptogenic?

FS lasting less than 10 or 15 minutes [2,14,89] have not been associated with subsequent epilepsy or cognitive deficits in prospective or retrospective studies [12,121,122]. However, the consequences of long FS, one of the forms of complex FS, are controversial [2,13]. Retrospective studies have linked a history of long FS and subsequent TLE [26,50,54,116]. Prospective studies generally failed to implicate long FS as causing TLE (see [105], for review), although careful review suggests that up to 40% of individual with long/focal FS developed epilepsy ([2]; Hesdorffer et al., personal communication). More recently, the FEBSTAT study, focusing on FSE, has begun to define abnormal EEGs, MRI changes and the development of TLE in children who have sustained FSE [72,93,107]. These findings, because of their prospective and careful design, are the strongest evidence to date about a causal relationship of FSE with TLE. However, children enter the study upon development of FSE. Therefore, predisposing factors of FSE, which might also predispose to TLE (or will affect the probability of FSE resulting in TLE) cannot be excluded. In other words, whereas FEBSTAT will answer the question of the development of epilepsy after FSE, and will delineate clear pre-existing factors such as cortical dysplasia or gene mutations, it will be difficult to establish a direct causal effect. To control for predisposing factors in the host brain requires animal models. Such models have been created for both individuals with predisposing factors (brain injury, dysplasia, ion channel mutations) and for a 'non-predisposed' host brain, and are described below.

### B. What is the role of predisposing elements of the host brain (gene mutations, cortical dysplasia) on epileptogenesis?

A large body of literature has addressed the potential genetic basis of FS [11,35,46,55,75,128], and the hypothesis that characteristics of the brain of the child who has a long FS govern if the child will develop epilepsy. FS run in families [15,16] but are also more common in children in day-care centers [17], and their generation is likely a result of both genetic and environmental causes that vary in each individual [11,25,47]. In several clear instances, specific mutations predispose to both FS development and subsequent epilepsy, including sodium and chloride channel mutations [3,46,101,128]. These mutations generate the "generalized epilepsy with febrile seizures plus" syndrome (GEFS+) of familial FS and/or several types of epilepsy. Cortical dysplasia has also been implicated in the development of epilepsy after FS [111].

Similarly, animal models of cortical dysplasia [51] and prior injury [99] suggest that FS affect the injured brain differently, including the probability of generation of epilepsy.

Elegant studies in mice genetically engineered to express human mutations such as of sodium channels involved in the GEFS+ syndrome and its extreme form, severe myoclonic epilepsy of infancy (SMEI) [77,78,90], demonstrated increased sensitivity to hyperthermia-induced seizures. Additional *in vitro* studies have begun to provide the underlying mechanisms [4,20,65,66,109,110,117,129]. Thus, both human and animal data are consistent with the idea that characteristics of the host brain contribute to the development of FS and to their consequences.

However, FS occurs throughout the world in generally 'non-predisposed' children who have no evidence of preexisting injury, brain-affecting gene mutations, or cortical dysplasia. Therefore, an important clinical question is whether FS can generate TLE in generally 'normal' children. If so, then the potential specific characteristics of the seizures that predict epileptogenesis should be studied.

### C. What parameters of the FS themselves (duration, severity) govern the development of epilepsy?

In children, simple FS are defined as short (< 10 or 15 minutes), and without focal features. The vast majority of epidemiological studies suggest that these FS are not associated with epileptogenesis [2,12,89]. Complex FS are defined as seizures that are long (> 10–15 minutes), or with focal features (e.g. involvement of one side of the body), or recur within 24 hours of the first episode [2,88] or within the same febrile illness [23]. In addition FSE is generally defined as FS longer than 30 minutes [93,107]. (Note: Scott et al. [102,103] define seizures lasting more than 30 minutes in normal children without intracranial infection as prolonged FS rather than FSE). It is these long and focal FS that are statistically associated with epileptogenesis, and the major correlation has been with the duration of the seizures [87,93,102,103,107,120]. However, the duration of FS in itself might also be an indication of a subtle abnormality of the host brain that interferes with stopping of the seizure [105]. Thus, in children, it is difficult to study if the duration of the FS itself is important for epileptogenesis. Duration of seizure is a crucial parameter in the adult brain; SE results in major changes in neuronal physiology (e.g., [53,74]). Thus, duration of FS is a logical candidate to contribute to the initiation of an epileptogenic process.

In animal models, duration of FS can be controlled experimentally. Dubé et al. initially used seizures of ~20 minutes, recapitulating "complex FS" [36,40]. More recently, the group used FSE-like seizures, and found that seizure duration influenced the incidence of limbic epilepsy and also governed the severity of the resulting spontaneous seizures (Figure 1a,b and [44]). Whereas shorter FS led to spontaneous seizures lasting seconds, experimental FSE led to longer seizures with robust motor phenomena (Figure 2). Other groups also employed models generating seizures lasting either ~20 minutes [31,32,61,70,71], or shorter single seizures [33,62,100], or a series of nine short FS [27,28]. The subsequent incidence of limbic epilepsy has not been examined in most of these studies. Scantlebury et al. [100] investigated this outcome in normal versus injured brains, and found that 86% of the rats that experienced cortical focal lesions and FS became epileptic in adulthood.

In conclusion, a body of clinical work spanning decades has suggested that FS duration might contribute to the probability of epileptogenesis. The FEBSTAT study, that includes children with FS longer than 30 minutes, has to date found epileptogenesis only in children whose seizures were ~an hour long (Shinnar, personal communication). Animal models have controlled for potential host brain confounders and established that FS duration is an important parameter for epileptogenesis. Thus, a preventive approach to FS-provoked epileptogenesis involves prevention of long FS by aborting the seizures with methods such

as using benzodiazepines. This is reasonable for a second or third seizure, but is obviously not feasible for the first FS.

## **D. How does epilepsy arise after FS? The role of cell loss, inflammation and altered patterns of gene expression**

### **Is epileptogenesis associated with cell loss?**

One of the structural hallmarks in patients with mesial TLE and a history of long FS is a specific pattern of cell loss in hippocampus, i.e mesial temporal sclerosis (MTS), and a reorganization of the remaining circuit [34,59,79,85,114]. These changes are considered by many to be required for epileptogenesis [7,91,108]. The nature of the relationship between cell loss and epileptogenesis in humans after long FS remains unclear. It has been widely hypothesized that FS cause MTS and the development of TLE is a consequence of MTS [93,103,120]. However, the clinical literature also supports the alternative view that TLE after FS might precede MTS, and the latter results from the epileptic seizures [67,86,96,106].

In animal models, early injury of neurons in hippocampus was found, that mirrored the distribution of cells that are lost or damaged in TLE/MTS (Figure 3). Interestingly, these cells seemed to recover over time, so that a significant loss of neuronal populations in hippocampi of rats was not found following single [9,100] or repeated episodes of FS [27], including in rats that became epileptic [40,44]. Although the methods employed (cell counts) cannot exclude subtle loss of some hilar interneuron populations, these data support the notion that cell loss is not a prerequisite for epileptogenesis. These findings are consistent with the presence of epileptogenesis without significant cell loss in other models in immature and adult rats [8,69,94,131]. In addition, Dubé et al., found increased hippocampal MRI signals in a subpopulation of rats that experienced FS [37,43]. These T2 changes were not associated with increased water content (Dubé, unpublished observations) or accompanied by neuronal loss in the hippocampus. These findings support three concepts: First, functional alterations of neuronal and network properties might take place in the absence of long-lasting structural changes (e.g. cell loss, sprouting), and result in epilepsy. Second, the MTS found in individuals with TLE and a history of FSE might not necessarily be a cause of the epilepsy, but a consequence [67,81,96]. Third, the acute increased T2 relaxation time reported in children with FSE within days of the seizures [93,103,120] might not indicate acute cell loss.

### **Does inflammation contribute to epileptogenesis that follows FSE?**

Inflammation is emerging as a major mechanism that contributes to epileptogenesis in a number of clinical settings [18,19,82,124,125]. In the context of febrile seizures, fever not only increases brain temperature, but also involves the release of inflammatory mediators, particularly cytokines [1,24,95,123,124] such as interleukin-1 $\beta$  (IL-1 $\beta$ ), within the brain. In children, higher levels of this cytokine in cerebrospinal fluid and/or plasma have been detected in individuals with FS by some groups [56,126] but not by others [68,118]. Some have implicated IL-1 $\beta$  in TLE with MTS [64], including a mutation in the IL-1 $\beta$  gene promoter [64,127]. It is intriguing that fever of specific infectious etiologies, and specifically human herpes virus 6 (HHV6) might influence the probability of generation of FS [5,130]. Whether this virus leads to higher levels or a unique profile of cytokine induction in the child's brain compared with other pathogens has not been studied, though evidence of HHV infection has been found in tissue from individuals with TLE [48].

In animal models, the involvement of endogenous IL-1 $\beta$  in the generation of FS was supported by the increased threshold temperature required to elicit experimental FS in mice

lacking the IL-1 $\beta$  receptor type 1 [39] and by the increased proportion of rats developing FS after lipopolysaccharide and kainic acid treatment [58]. As mentioned above, IL-1 $\beta$  may contribute to the generation of FS in human infants. However, whether or not IL-1 $\beta$  contributes to the epileptogenic process that is triggered by FS remains unclear. Dubé et al., found that IL-1 $\beta$  expression was induced in reactive astrocytes for at least 24 hours after FSE and returned to basal levels within 72 hours [44]. Interestingly, when FS-experiencing rats that became epileptic were compared to those in which the inciting FS did not lead to spontaneous seizures, hippocampal IL-1 $\beta$  levels were higher only in rats that developed epilepsy (ibid).

### **Coordinate changes in the expression of numerous genes may contribute to the epileptogenic process**

Experimental FSE induces numerous molecular changes (reviewed in [41]; [83]). Among them, lasting changes in the expression of specific genes such ion channels and endocannabinoid receptors have been explored to date. Notably, hyperpolarization-activated cation channels (HCN) have been implicated not only in FS [29,30], but in other models as well [45,63,76,92,97]. Seizures induce a long-lasting reduction of HCN1 isoform expression [21,22]. The precise mechanisms by which alterations in HCN channels and I<sub>h</sub> contribute to human epileptogenesis are not fully known; however, HCN1 channel expression was altered in a subset of resected hippocampi from patients with TLE and MTS, often with a history of early life seizures [10]. Mutations in HCN channel genes have recently been discovered in individuals with epilepsy [35], further supporting the role of these channels in the epileptogenic process.

Similarly, increased endocannabinoid receptor levels inducing a short-term plasticity phenomenon has been described [31,32]. Altered expression of other genes may also play a role [27,38,57].

Whereas the changes in the expression of the above specific genes have been studied in detail, recent evidence supports massive, coordinate transcriptional regulation of hundreds of genes to be involved in the epileptogenic process that follows FSE. These changes may underlie the mechanisms by which FSE initiate the transformation of 'normal' neurons and neuronal circuits into epileptic ones. Activation of specific transcription factors by seizures which regulate select gene clusters, may contribute to epileptogenesis. One candidate is the neuron-restrictive silencer factor (NRSF) that was recently shown to be involved in FS and other models [6,52,84,115]. Studies are underway to determine which genes are regulated by NRSF and the role of this transcription factor in epileptogenesis that follows FS. Therefore, identifying key genes that may contribute to the development of epileptogenesis and delineating the mechanisms that regulate these genes may provide molecular targets for the development of novel therapeutic strategies for preventing the development of TLE after FS.

### **E. Predictive biomarkers of epileptogenesis**

If FS lead to TLE, this process arises only in a subset of children. Defining predictive biomarkers to identify the individuals experiencing long FS and/or FSE that are risk for epilepsy is critical and should provide a powerful tool for testing of potential interventions. MRI changes and EEG activity alterations could constitute excellent biomarkers because they can be quantified and repeated.

Early MRI changes, specifically, increased T2 signal arising within days after long FS in children, have been described [93,103,120]. In early studies of EEG that were obtained within a week after FS, Frantzen et al. [49] described abnormalities, mainly focal or global slowing, in about a third of the EEGs. However, the presence of an abnormal EEG did not



correlate with seizure recurrence [49,113] or with the subsequent development of epilepsy [49]. More recently, the FEBSTAT study, focusing on FSE, has begun to define MRI changes (increased T2 signal) and abnormal EEGs (focal slowing) in children who have sustained FSE. The study plans to correlate these changes (as well as subsequent hippocampal volume loss) with the development of TLE. These are important and powerful clinical approaches; however it would be difficult to exclude factors that predispose to the occurrence of FSE and/or to the development of TLE in human studies. In addition, the development of TLE after FSE often involves time periods lasting a decade or more [50,80].

In this context, predictive animal models of FS-provoked epileptogenesis are useful. Using MRI, Jansen et al. found increased T2 values early (within 24 hours) after experimental FS, as did Dubé et al. [37]. Reduced apparent diffusion coefficients in hippocampus and other limbic structures 24 hours after FS were also apparent in the Jansen study [61]. The MRI alterations in that study persisted up to 2 months after FS, but the group did not correlate the MRI changes with epileptogenesis. Direct correlation of early FSE-induced MRI changes with subsequent epileptogenesis was attempted by Dubé et al. [43,44] who imaged controls and rats that experienced FSE one month later, and found increased hippocampal T2 relaxation times in a subset of FS rats [44]. However, T2 values did not distinguish the rats that developed limbic epilepsy from those that did not, though these T2 values correlated with interictal activity. Interestingly, the same group found that augmented T2 values one month after the FS correlated with hippocampal dysfunction manifested as spatial memory deficits [43]. Another potential biomarker, interictal activity, was investigated in the models of FS with a prior lesion [100] and of long FS and FSE [40,44]. Whereas Scantlebury and colleagues detected the presence of interictal activity (spikes and epileptic discharges) only in rats that developed limbic epilepsy (86%), Dubé et al. found that interictal activity arose in ~90% of the rats after FSE, while ~45% of the rats became epileptic. No rat became epileptic without interictal activity; however, the presence of such activity did not predict epileptogenesis. Interestingly, EEG spectrum analysis revealed that a significant reduction of energy in the low frequencies (delta and theta range) distinguished epileptic rats from controls and those with interictal activity alone [40].

The possibility that inflammatory molecules might constitute biomarkers for epileptogenesis has been investigated by several groups. Sharp (e.g., [73,104]) investigated the gene expression profile in peripheral white blood cells one day after kainic acid seizures, as well as after other insults, and found unique gene-expression patterns for each of the experimental conditions. In the context of FS, Sasaki et al. [98] examined the induction of genes related to inflammatory mediators and ion channels in leukocytes of a small number of children with FS and controls. They stimulated these cells with a Toll-like receptor agonist, synthetic double strand RNA. The expression of a number of inflammatory genes, among them IL-1 $\beta$ , was enhanced in children with FS compared to controls, suggesting a modified inflammatory response. It would be interesting to examine if differences in gene expression or induction in peripheral white blood cells (especially inflammatory mediators) distinguish individuals (rats and children) that develop epilepsy after FSE from those that would not. In a rat model, significantly higher levels of IL-1 $\beta$  were detected in the hippocampi of rats with FSE compared to controls 24 hours after the seizures, and, as mentioned, high IL-1 $\beta$  levels distinguished FSE rats that became epileptic from control rats [44]. These data lead to the speculation that if feasible and validated, detection of IL-1 $\beta$  in the periphery might provide an interesting and potentially clinically relevant biomarker.

## F. What therapeutic strategies can be used for preventing and/or reversing FS-induced epileptogenesis?

The evidence summarized here indicates that long FS and FSE may provoke epilepsy. In addition, the duration of the FSE seems to be an important determinant of the development of subsequent limbic epilepsy in the non-predisposed brain (Figure 1). These findings suggest that preventing long FS should be a therapeutic goal. In addition, because it is clinically not feasible to abort all long FS and FSE, identification of children at risk for epileptogenesis should lead to preventive measures. At the present time, no single mechanism has emerged to account for FSE-induced epilepsy in the non-predisposed brain. As discussed above, inflammation is implicated and will likely be a subject of preclinical and clinical studies [124].

In summary, much has been learned over the past decade about the epileptogenesis that follows FS. Both clinical and experimental studies have addressed several key questions, and established that very long FS and FSE provoke changes in the brain that promote epilepsy. These changes take place at multiple levels, are likely driven by transcriptional mechanisms, and are potentially induced by inflammatory mediators. The discovery of early predictive biomarkers is crucial; these biomarkers, together with elucidation of the epileptogenic mechanisms will provide avenues for prevention and intervention.

## Acknowledgments

The authors thank Mrs. Barbara Cartwright for excellent editorial help. Supported by NIH grant R37 NS35439 and NS35439-S1 (ARRA).

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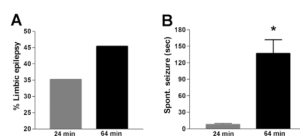
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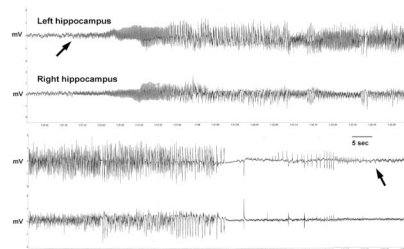


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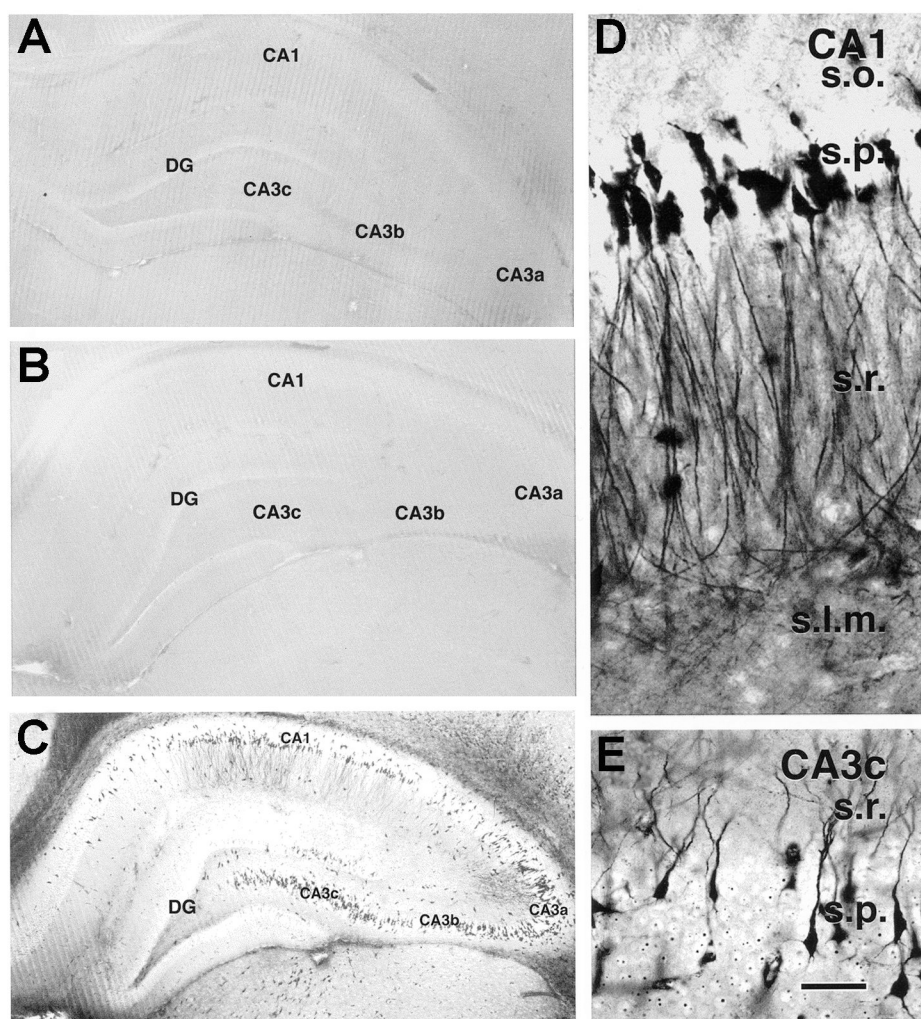


**Fig. 1.**

The duration of FS influenced the probability of developing limbic epilepsy and the severity of the resulting spontaneous recurrent seizures. (A) The percentage of rats developing limbic epilepsy increased by 30% after a 64 minute FS compared to a 24 minute FS. (B) The duration of FS affected the duration and the severity of the resulting spontaneous seizures: Mean duration of seizures was significantly longer ( $136.7 \pm 25$  sec,  $n = 18$ ) after a 64 minute FS compared to a 24 minute FS ( $7.8 \pm 0.3$  sec,  $n = 57$ ; median durations, 91 vs 7 sec). Modified from [44], with permission.



**Fig. 2.**  
Example of spontaneous electrographic seizure recorded from hippocampal bipolar electrodes in adult rats that experienced a 64 minute FS. Arrows point to onset and end of epileptiform discharges. Calibration: 5 sec. Dube et al., unpublished; please see [44] for methods.



**Fig. 3.**

Cell injury in the same distribution as found in MTS is transiently provoked by experimental long FS. Using a modified Golgi stain, silver uptake was found in populations of hippocampal neurons in rats that experienced FS (C) compared with normothermic (A) and hyperthermic (same duration of hyperthermia but no seizures; B) controls. Note abundant stained neurons in CA1 (Sommer's section) (D), CA3 and the hilus (E), as demonstrated here. Serial evaluation of hippocampi between 24 hours and 4 weeks demonstrated gradual resolution of this cell injury without apparent cell loss [from 119, with permission], Scale bar: 50  $\mu$ m.